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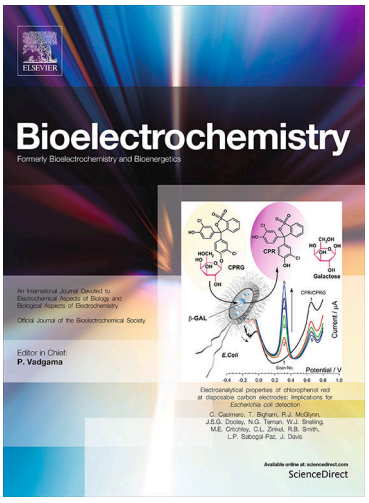

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Clinical considerations of bleomycin based electrochemotherapy with Variable Electrode Geometry electrodes for inoperable, deep-seated soft tissue sarcomas

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Judit Olah and **Gabriella Erika Kis** are both last authors with equal contribution to the current manuscript.

Abstract

The aim of the current prospective pilot study exclusively for deep-seated soft tissue sarcomas (STS) was to evaluate efficacy and safety of bleomycin-based ECT using VEG (variable electrode geometry) electrodes. During a 2-year period, seven surgically inoperable STSs were treated at the University of Szeged, Department of Surgery in Hungary. Electrode placement was determined by software planning using preoperative imaging (CT/MRI) and intraoperative ultrasound. Intravenous bleomycin (15000 IU/m2) was administered 8 minutes before first pulse generation which lasted up to 40 minutes. Tumour response was evaluated through CT/MRI 2 months after treatment as per RECIST v.1.1. Five male- and 2 female patients were treated with fibromyxoid sarcoma (n=2), epitheloid sarcoma (n=3), liposarcoma (n=1) and myofibroblastic sarcoma (n=1) with median age of 54 years (49-88). Median tumour diameter, tumour volume and tumour depth was 5.9 cm (3.7-22.5), 131.13 cm3 (35.6-2456.22) and 6.18 cm (3.74-18.18), respectively. Median operative time was 75 min (35-180), median hospital stay 2 days (2-20). Two month follow-up confirmed partial response in 5 patients, while stable disease in 1 patient, and progressive disease in 1 case as per RECIST v.1.1. Grade 2 ulceration

was experienced in four cases, and a transient left musculus quadriceps femoris plegia occured in one patient. Local control of deep-seated STSs with BLM-based VEG ECT holds a promising perspective and our results may serve as a practical guide for further investigation and treatment planning.

Key words: electrochemotherapy, soft tissue sarcoma, deep seated, variable electrode geometry

Introduction

Soft tissue sarcomas are a heterogenous group of tumours accounting for more than 100 entities with unique clinical and histopathological subtype features arising from extra-skeletal and skeletal connective tissues [1]. Soft tissue sarcomas are rare tumours, accounting for about 1% of all adult human cancers and 15% of pediatric malignancies [2]. They can occur at any part of the body most often on the extremities (59,5%), less frequently in the retroperitoneum and the trunk [3]. Due to high local recurrence rate and excessive metastasis-forming properties, a sufficiently wide and deep surgical excision is decisive for accurate prognosis. Radiation- and systemic chemotherapy are also important pillars of therapy [4,5]. Treatment and care of diagnosed patients requires multidisciplinary approach, preferably in an oncology center where materials and technical conditions necessary for both diagnosis and therapy are available [6]. The efficacy of ECT has already been proven in the treatment of cutaneous STSs [7, 29]. With the development of long needle electrodes even problematic, deep situated tumours, otherwise not suitable for surgery can become accessable.

Electrochemotherapy carried out with reversible electroporation (EP) is a technique during which cell membrane permeability increases through induction of high intensity electric pulses, leading to increased penetration of hydrophilic molecules such as citotoxic agents (bleomycin [BLM]) [8]. During EP, cytotoxicity of BLM inside the target tissue can be raised up to 10000 fold, making it by far the most acquired drug for electrochemotherapy (ECT) [9,10]. Well documented effects of ECT include three key elements of targeted actions: first, a direct concentration-dependent citotoxic effect on tumour cells, second a “vascular lock effect", with prompt local vasoconstriction through precapillary sphincters keeping the given drug inside the target tissue, and a time delayed damage in tumour vasculature, causing disruption in tumour blood flow [11]. The third, is a so called vascular disrupting effect, leading to uptake of citotoxic agents by tumour stromal cells and leading to endothelial cell death. Standard ECT has been successfully used for decades in the treatment of superficial tumours for various histotypes with 80% OR rate (objective response rate) and mild side effects. [12,13,14,15,16].

Application of ECT for deep-seated tumours opened up a completely new horizon in the treatment of advanced, surgically incurable tumours. Promising results of ECT including STSs have previously been reported, in cohorts together with different tumour histotypes (malignant melanoma, Merkel cell carcinoma, colon-, or lung adenocarcinoma, soft tissue sarcoma) [17,18]. Studies describing VEG ECT treatment exclusively for soft tissue sarcomas

have not been previously reported, mainly due to rarety of lesions, consecutive low number of patients and extremily high number of histological subtypes [19].

Treatment considerations are similar to standard ECT, including selection of the most adequate electrode type (standard-fixed geometry vs variable electrode geometry) for sufficient electric field coverage of complete tumour volume (Figure 1 and 2) and the presence of the citotoxic agent inside the target tissue. Deep-seated lesions encompass a variety of bulky, extended tumours, mostly involving types not candidate for surgical resection. Soft tissue sarcomas, if reaching the skin can be accompanied by bleeding (oozing), pain, odourous discharge which affect patient quality of life on a daily basis.

Each STS subtype represents specific morphology, biological behaviour, sensitivity to medications and prognosis, hence gathering and analysis of such rare occurring lesions comprise major challenges in research and treatment planning [20,21]. Despite surgical resection and chemo-radiation applied as the first line of treatment, STSs recur in 50%<, frequently with distant failure [22]. The aim of our study was to assess tumour response, safety and side effects of BLM-based VEG ECT for STSs, and describe operative- and perioperative outcomes with technical challanges of treatment. Due to advanced stage of included lesions, the primary treatment goal was to maintain best possible results for local tumour control. Our publication describing initial results is a first-in-line study of BLM-based VEG ECT, exclusively applied for deep-seated soft tissue sarcomas.

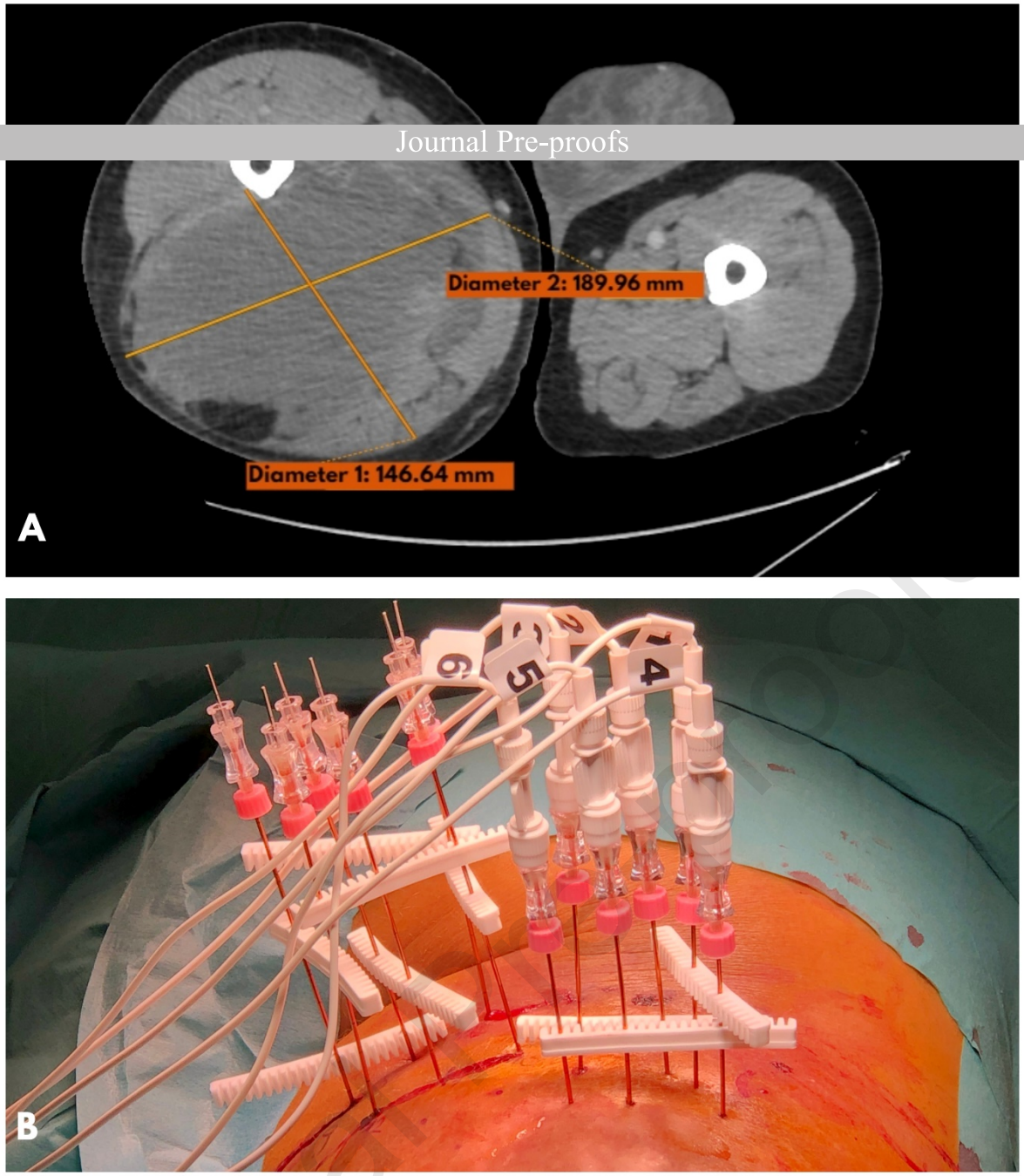

Figure 1: VEG ECT treatment of fibromyxoid sarcoma of the left lower extremity (thigh). A: MRI showing pretreatment extent of the sarcoma. B: electrode positioning during VEG ECT treatment. ECT: electrochemotherapy; MRI: magnetic resonance imaging

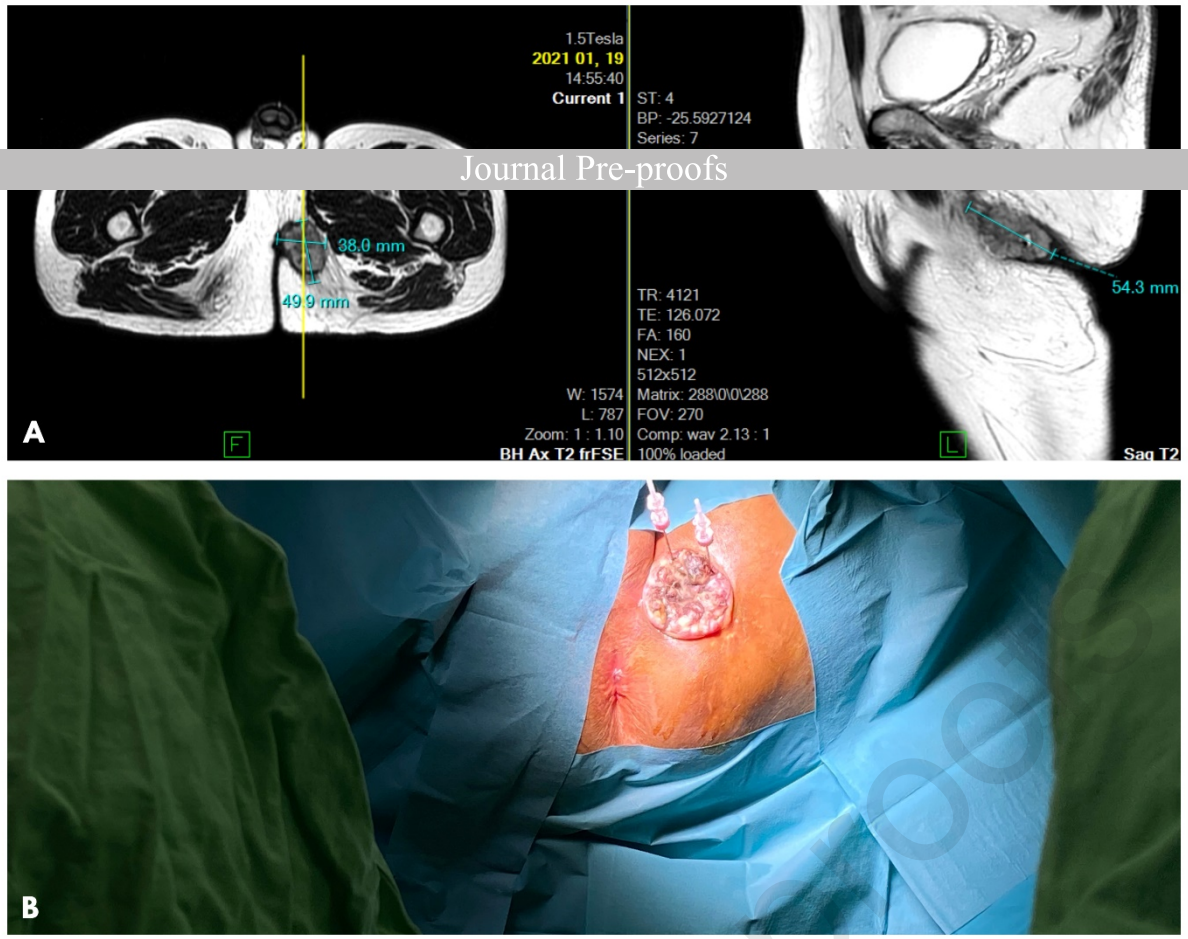

Figure 2: Epitheloid sarcoma of the left gluteal region. A: MRI showing pretreatment extent of the sarcoma. B: Initial electrode placement during VEG ECT treatment. ECT: electrochemotherapy; MRI: magnetic resonance imaging

Materials and Methods

The current prospective observational pilot study was conducted at the University of Szeged, Faculty of Medicine, Hungary.

Patient selection

Based on multidisciplinary institutional tumour board (University of Szeged) decision, patients with advanced, surgically inoperable, soft tissue sarcomas were enrolled in the study. Deep-seated tumours with axial diameter at least 3 cm and depth (from skin to deepest tumour margin) not exceeding 20 cm were included. Inclusion criteria had to meet ECOG scores of 0-1, with potential life expectancy of 3 months, or higher. International normalized ratio (INR)

of <1.5 was mandatory, hematological consultation was needed in case platelet count < 70.000/mm^3. Serum creatinine < 150 µmol/l.

Exclusion criteria included the following: pregnancy, breast feeding, hypersensitivity- or allergy to bleomycin, cumulative dosage of bleomycin exceeding 400.000 IU, se creatinine > 150 µmol/l, unbalanced coagulation abnormality (anticoagulation therapy incompatible with surgery), inevitable electrode contact with a pacemaker, chemotherapy applyed one week prior to-, or due one day after ECT treatment.

The study was approved by the Regional and Institutional Review Board of Human Investigations at the University of Szeged , Hungary, approval number (ECT-REPRO-002). Indication for ECT was discussed and agreed on prior to each procedure with the multidisciplinary ECT tumour board and all patients provided signed informed consent.

The primary objective was to evaluate response rate of ECT treatment for deep-seated STSs using VEG electrodes. Response was individually evaluated in case of each treated STS by radiological imaging prior to and 2 months after treatment. Tumour response was evaluated according to response evaluation criteria in solid tumours (RECIST), v1.1. Complete response was confirmed when the target lesion completely disappeared, PR in case of 30% decrease in diameters, PD in case absolute increase of existing lesions (min. 20%) and SD if neighter sufficient shrinkage for PR, nor increase for PD was noted [23].

The secondary objective was to register adverse events for ECT. Side effects were evaluated and categorized as Adverse Events or Serious Adverse Events according to CTCAE criteria version 4.0. Safety was evaluated through physical examinations before treatment and at follow-up visits. Pain score was provided by patients using a Visual Analog Scale (VAS) ranging from 0 to 10.

EuroQol-5 Dimension (EQ-5D-3L) questionnaire was used to evaluate patient quality of life influenced by ECT treatment.

Treatment plan and electrode placement

Each ECT treatment was carried out with Cliniporator Vitae (Cliniporator VITAE, IGEA, Carpi, Italy). Preoperative planning was based on CT (computed tomography), MRI (magnatic resonance imaging), or PET-CT (positron emission tomography). The number and configuration of electrodes with the exact distance between electrode pairs were determined by previous software planning (Pulsar software version 1.0) to achieve proper electrode positioning for complete tumour volume coverage and necessary levels of electric field. In case of lesions with a maximum diameter of more than 40 mm, VEG-electrodes (active tip: 30-, or 40 mm) were placed deeper along the calculated path with ultrasound (US) guidance after applying the first train of impulse, in order to reach the deepest point of the tumour and maintain treatment with at least 10 mm safety margin. Preoperative planning was finalized by a medical physicist, intraoperative US was carried out by a radiologist during each treatment to confirm adequate electrode placement. During the treatment of the retroperitoneal myofibroblastic sarcoma, in order to treat a relatively small (25x45 mm) tumour remnant, two sets of electrodes (2x6 electrodes) where placed through CT guidance, with CT images projected onto previous PET-CT images to match and target the tumour (Figure 3). In case of truncal tumour localisations, electric impulses were synchronized with patient ECG.

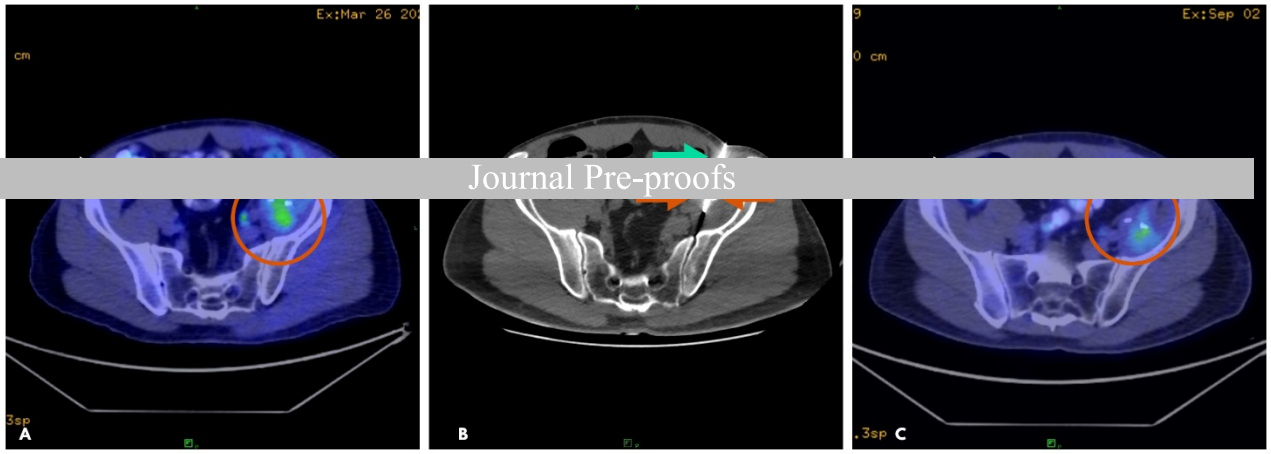

Figure 3: A: 18F-FDG-PET CT identical axial slices of remnant (remaining tumour tissue after surgery) myofibroblastic sarcoma before VEG ECT and C: after VEG ECT- tumour designated with red circle. B: NEC (non-contrast enhanced) CT for VEG electrode placement (green arrow) and metal clips placed as a hallmark for tumour margins during previous surgery (orange arrows). White arrows indicate physiological accumulation at the site of the coecum (A, C). Tumour volumes- A: preECT: 131.13 cm3, C: postECT: 86.78 cm3; volume change: -33.82% confirming partial response (PR) to treatment. Total lesion glycolisis (TLG) is a value that characterizes the complete size of the metabolically active tumour, which was calculated as metabolic tumor volume (MTV) multiplied by the mean sandard uptake values (SUV): preECT TLG : 251,21 g, postECT TLG: 178,97 g. VEG: variable electrode geometry; ECT: electrochemotherapy

BLM-based ECT treatment

Management of patients and BLM-based VEG ECT treatment were performed according to updated standard operative procedures (SOP) [24].

Treatment delivery success was evaluated intraoperatively during each BLM-based ECT session. Treatment was deemed successful in case the applied electric current characteristics were sufficent, which were evaluated through IGEA Viewer EPS02-VGP02 ver 2.2. (Figure 4)

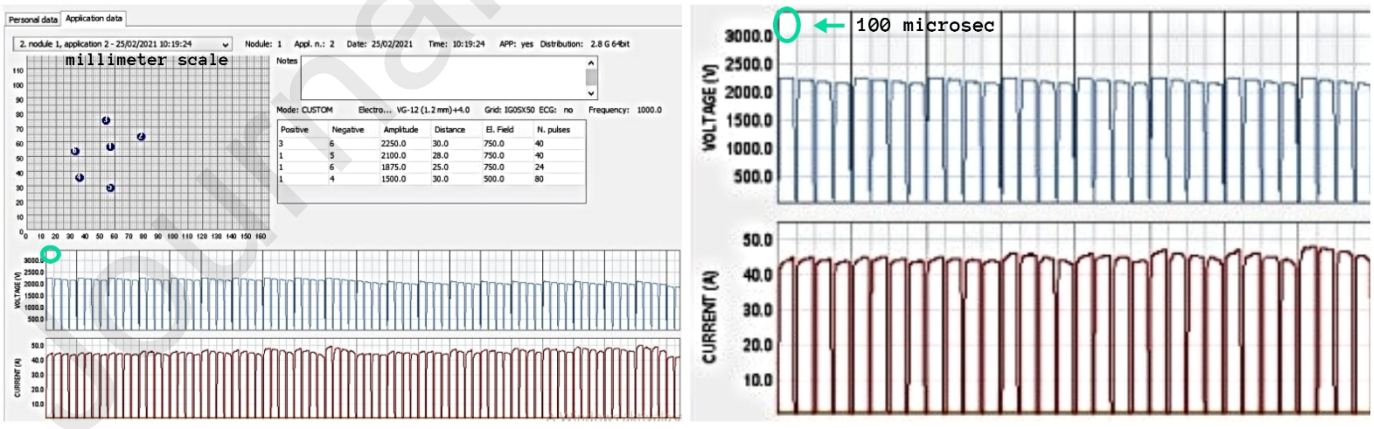

Figure 4: IGEA Viewer- displaying voltage (blue) and current (red) values for each VEG electrode pair in case of a 6-electrode treatment. Electrode placement can be seen on a millimeter scale (both axes)

in the left upper part of the image displaying electrode distance (range 5mm-30mm). In the right part of the image, voltage and current values of pulse durations lasting 100 microseconds can be seen (green circle and arrow). VEG: variable electrode geometry

Results

Enrolled patients Seven patients (5 male, 2 female) with histologically verified STSs were enrolled in our prospective study conducted between 2019 January-2021 March.

Median age was 54 years (49-88), with median ASA score (American Society of Anaesthesiologists) and CCI (Charlson Comorbidity Index) of 2 (2-3) and 5.5 (3-9), respectively (Table 1- Supplementary). Three patients with epitheloid sarcoma (1 left axilla, 2 left gluteal region), 2 fibromyxoid sarcoma (1 right axilla, 1 right lower extremity), 1 liposarcoma (right lower extremity) and 1 myofibroblastic sarcoma (left retroperitoneum) were treated with BLM-based VEG ECT. Tumour stages ranged from T3N0-T4N1. All patients received previous treatment prior to BLM-based VEG ECT, which included surgical removal (n=7; 100%), chemoradiotherapy (CRT) (n=4; 6.66%), radiation therapy (n=2; 3.33%), previous ECT (n=3; 50%) and immunotherapy (n=1; 16.66%) (Table 1- Supplementary). Preoperative median tumour volume was 131.13 cm3 (35.6-2456.22), median tumour diameter was 5.9 cm (3.7-22.5), with median tumour depth (skin to deepest point of the tumour) of 6.18 cm (3.74-18.18). Median time interval of ECT treatment from confirmed diagnosis of STS was 19 months (8-144). Median follow-up after ECT treatment was 7 months (2-18) (Table 2- Supplementary). Since all seven patients had advanced stage, deep-seated STSs, our primary intent was to achieve local tumour control, with the aim of reaching best possible response. Based on tumour features, each patient already had tumour related complaints such as bleeding, oozing, odour, or constant pain at the tumour site at initial presentation.

VEG-ECT treatment

Each treatment was carried out under general anaesthesia with intravenous administration of bleomycin (15000 IU/m2). Median operative time was 75 minutes (range: 35-180), median hospital stay 2 days (2-20). Every ECT treatment was performed using VEG electrodes and successfully completed in each case (Figure 3). Electrodes with active tips of 30-40 mm and electrode length of 16-20 cm (VGD-1230T16: 1,2mm/30mm/16cm, VGD-1230T16: 1,2mm/40mm/16cm, VGD-1230T20: 1,2mm/30mm/20cm) were applied. Six VEG electrodes were used during 3 (50%), and five electrodes during 1 (16.66%) treatment session. In two cases (33.33%), ECT was started with five electrodes adding one extra VEG electrode to adjust to tumour size (Table 3- Supplementary) (Figure 5). Twelve electrodes (2x6 electrodes) were applied during the CT guided treatment of one myofibroblastic sarcoma in the left retroperitoneum.

Repositioning and adjustment of electrodes were necessary during each treatment in order to properly cover tumour volume [median tumour volume 131.13 cm3 (35.6-2456.22)] and maintain safety margins (0.5-1 cm). In order to cover complete tumour extent, electrode repositioning was carried out in 6 cases (85.71%). Each pulse delivery and electric current characteristics were documented and evaluated during each procedure (Table 2-Supplementary). Median values were as follows: pulse repetition frequency 1000 Hz, median electrode distance 24,25 mm, median value of applied voltage 2066 V, median pulse duration

100 µsec, electric current 37.5 A (19.9-50), resistance 56.39 Ω, median current repetition 8 (Table 3- Supplementary). During and after the procedures, delivered pulse parameters were obtained in order to evaluate intraoperative data (IGEA Viewer EPS02-VGP02 ver 2.2.) (Figure 4).

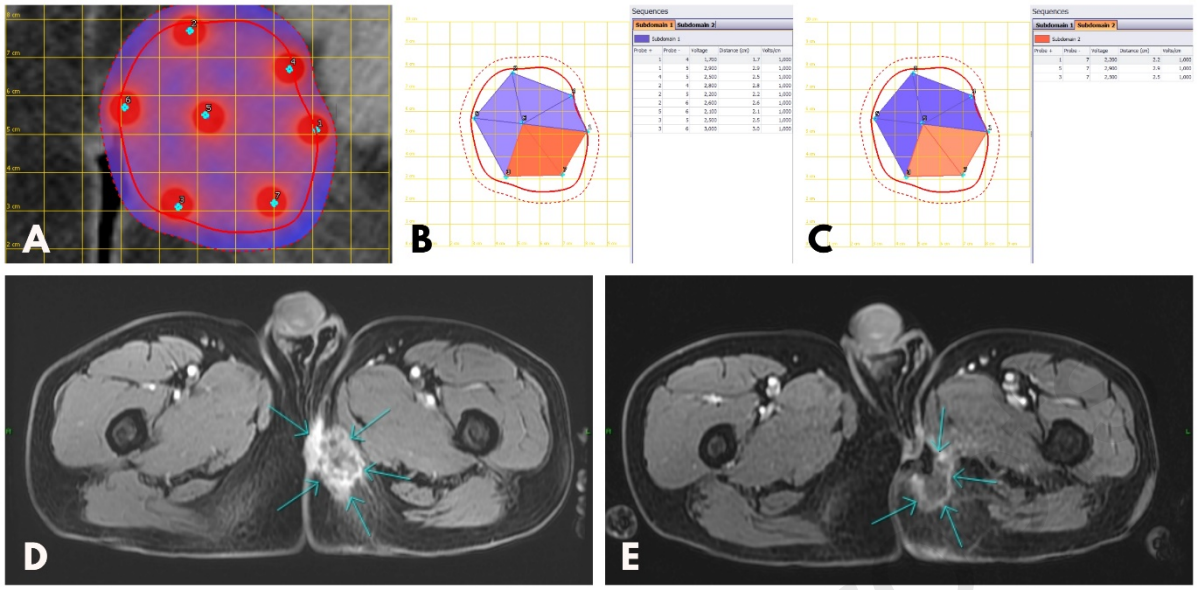

Figure 5: Treatment planning for VEG ECT for T4N1 epitheloid sarcoma of the left gluteal region. A: preECT electrode placement planning through Pulsar software. B, C: electrode placement and electrode repositioning with section (subdomain) 1 (purple) and -2 (orange) for sufficient current coverage and safety zones (red lines). D, E: MRI- axial T1-weighted 3D measuring after Gadolinium. D: preECT- venous phase image- arrows showing inhomogenous contrast enhancement at the sides of the tumor. E: postECT- central tumor necrosis, with only marginal enhancement and wide tissue absence on the medial side of the gluteal muscle. [preECT tumor volume: 249.11 cm3 vs postECT tumor volume: 61.1 cm3; volume change: -75.48%]. VEG: variable electrode geometry; ECT: electrochemotherapy; MRI: magnetic resonance imaging

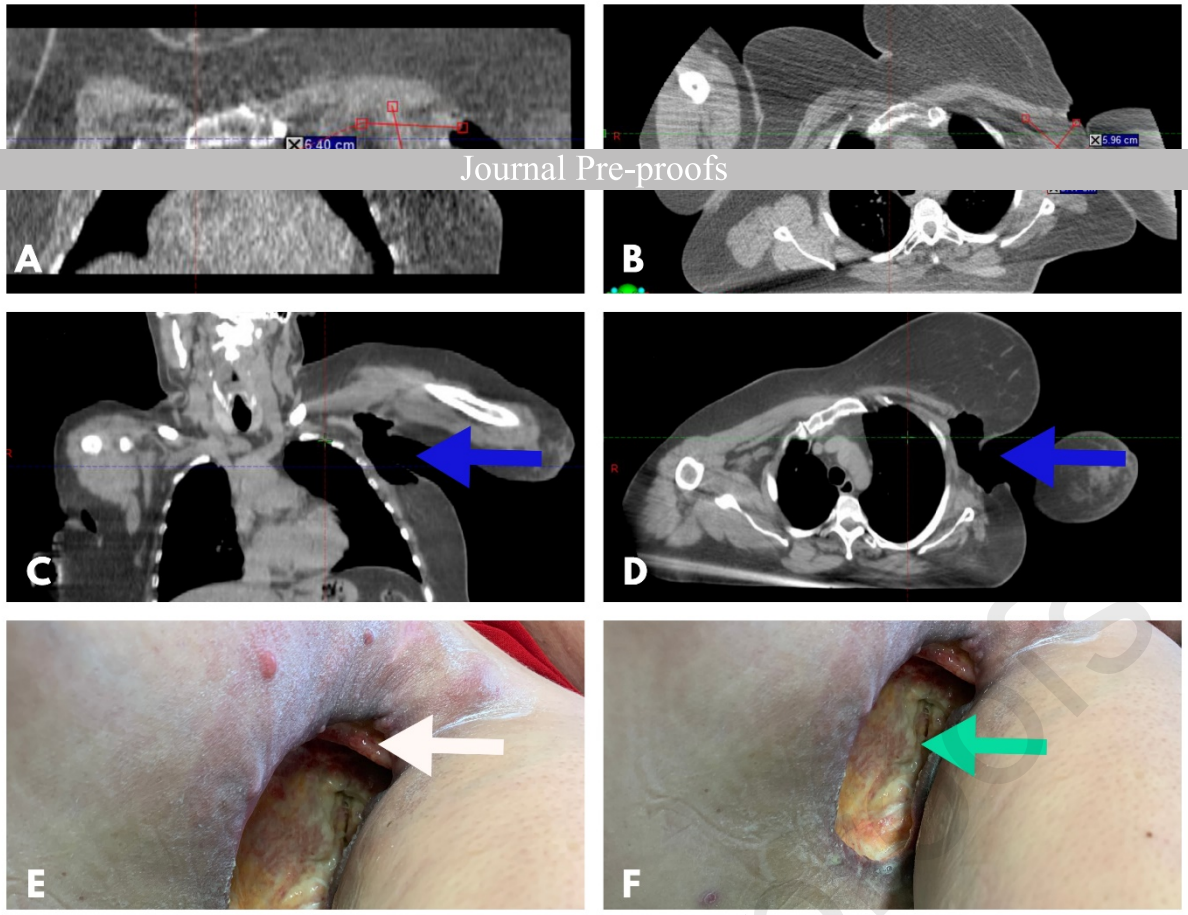

Figure 6: T3N1 epitheloid sarcoma of the left axilla. A, B: preECT coronal and axial CT showing tumor diameters; C, D: 2-month follow-up coronal and axial CT confirming partial response (blue arrows). [preECT tumour volume: 82.4 cm3 vs postECT tumour volume: 39.1 cm3; volume change: -52.55%]- non-contrast enhanced CT scan images. E: postECT image of left axilla with edge of pectoralis major muscle (white arrow), and F: cavity after necrotic tumour tissue removal. Plastic surgery- closure of cavity with advancement flap was planned, unfortunately the patient deceased prior to surgery. ECT: electrochemotherapy; CT: computed tomography

Response evaluation

Radiologic evaluation. Two months after treatment, tumour volume was determined by the same, preoperatively used radiological imaging modality (CT/MRI/PET-CT). According to RECIST v.1.1. partial response was seen in 5 (71.42%) (Figure 4,5,6), stable disease in 1 (14.28%) and progressive disease in 1 (14.28%) case (Table 4,5). Partial response was seen in two cases of epitheloid-, 1 fibromyxoid-, 1 lipo- and 1 myofibroblastic sarcoma. Both tumours involving the lower extremity were confirmed PRs (1 fibromyxoid-, and 1 liposarcoma). Interestingly, highest median tumour volume was seen in PR cases (131.13 cm3), lowest in PD, which was considerably higher in SD (PD vs SD: 35.6 vs 303.2 cm3). Median tumour depth (deepest point of the tumour from the skin) was 10.842, 3.74 and 9.71 cm for PR, PD and SD, respectively (Table 4,5).

Four patients (3 PR and 1 PD patient) were still alive at data evaluation (postECT follow up: 3 PR: 20, 16 and 7 months, PD: 4 months). After BLM-based VEG ECT one patient continued

immunotherapy with nivolumab and one received mono-ADM (doxorubicin) palliative chemotherapy.

Interestingly the largest median tumour volumes (131.13 cm3) were seen in PR cases (n=5), with tumours situated in the lower extremities (n=2), axilla (n=1), gluteal region (n=1) and

Smallest tumour depth (3.74 cm) was found in PD (n=1) and included previous surgical resection, chemoradiotherapy and ECT with current VEG ECT carried out using 6 electrodes.

	PR (n=5)	**PD (n=1)**	**SD (n=1)**
Histology			
fibromyxoid sarcoma	1		1
epitheloid sarcoma	2	1	
liposarcoma	1		
myofibroblastic sarcoma	1		
Anatomical location			
axilla	1		1
lower extremity	2		
gluteal region	1	1	
retroperitoneum	1		
Median tumour diameter (cm)	8.7	3.8	9.1
Median tumour volume (cm3)	131.13	35.6	303.2
Median tumour depth (cm)	10.842	3.74	9.71
Previous oncological treatment			
Surgical resection	5	1	1
CRT	3	1	
RT	1		1
ECT	1	1	
IT	1		
Number of electrodes			
twelve (2x6 electrodes)	1		
five			1
six	2	1	
five+1	2		
Ulceration			
YES	4	1	1
Oedema			
YES	5	1	1

Table 4: Tumour characteristics related to tumor response. PR: partial response; SD: stabile disease; PD: progressive disease; CRT: chemo-radiatiotherapy; RT: radiationtherapy; ECT: electrochemotherapy; IT: immunotherapy.

patient	imaging	preECT tumour volume (cm3)	2 month postECT tumour volume (cm3)	volume change (%)	response as per RECIST 1.1
II.	CT	99.6	67.63	-32.1	PR
III.	CT	2456.22	1581.81	-35.6	PR
IV.	MRI	249.11	61.1	-75.48	PR
V.	CT	303.2	363.23	+ 19.8	SD
VI.	MRI	35.6	69.0	+ 93.82	PD
VII.	PET-CT	131.13	86.78	- 33.82	PR

Table 5: Baseline tumour volumes prior to ECT and changes after 2 months with follow-up imaging as per RECIST v1.1. PR: partial response; SD: stabile disease; PD: progressive disease; ECT: electrochemotherapy, CT: computed tomography; MRI: magnetic resonance imaging, PET: positron emission tomography.

Adverse Events

Postoperative ulceration was seen in 4 cases, (CTCAE Grade 2). Improvement of clinical complaints (bleeding, oozing, odour, pain) was seen during each case (Table 2-Supplementary). On the basis of the EQ-5D-3L with elapsed time after ECT, most patients showed improvements in quality of life with decreasing postECT pain levels. One serious adverse event occured during the CT-guided ECT treatment of a left sided retroperitoneal myofibroblastic sarcoma. On the 1st postoperative day the patient experienced tingling of the treated area with considerable swelling. On the 2nd postoperative day paresis of the left thigh was observed, the patient was unable to lift his leg. Patient was referred to a neurologist, and iv steroids (Solumedrol 125 mg for seven days), Thiogamma and Bentfogamma were administered. MRI confirmed extended swelling of the treated area, which partially resolved during the next 1 month. With regular phisiotherapy after discharge the patient regained most of the movements without any mention of additional pain. Follow-up PET-CT confirmed partial response of the treated sarcoma (Figure 7).

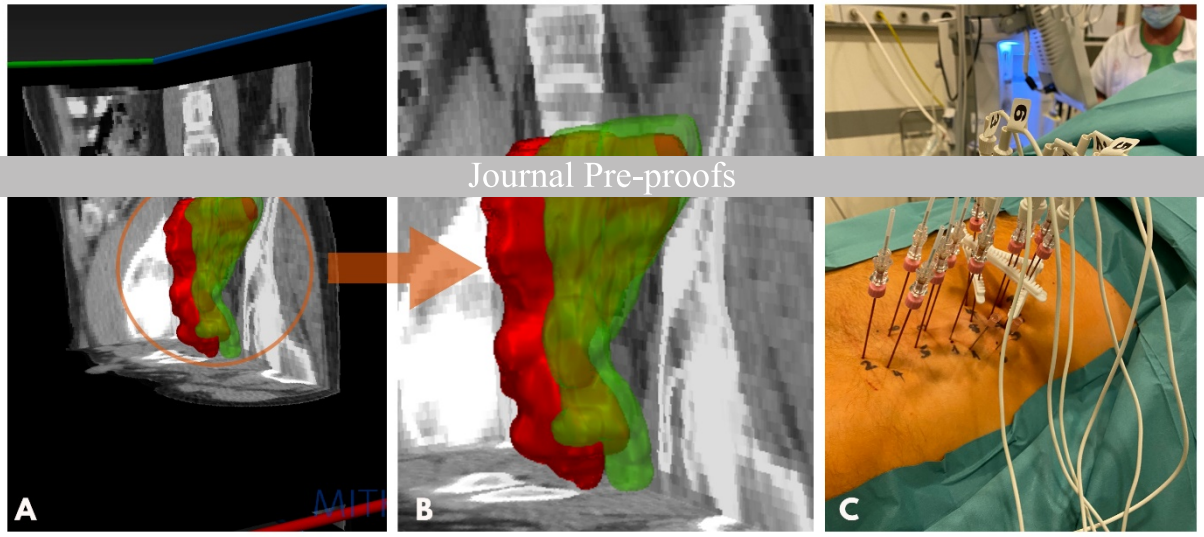

Figure 7: A, B: 18F-FDG PET-CT/MRI fused 3D metabolic tumour volumes of a myofibroblastic sarcoma in the left retroperitoneum (red: pretreatment tumour volume; green: posttreatment tumour volume) with decreased postECT volume mainly at the medial side. C: CT- guided placement of VEG electrodes during ECT. ECT: electrochemotherapy; PET: positron emission tomography; CT: computed tomography; MRI: magnetic resonance imaging

Discussion

Bleomycin based ECT emerges as an effective local anticancer therapy including a wide range of tumour types, with curative or palliative intent and considerable improvement in patient quality of life.

In order for ECT treatment to be effective and reach tumour boarders maintaining sufficient electric field, careful patient selection and an accurate choice of electrodes is essential. With the use of long needle electrodes, deep situated tumours have become accessible. VEG ECT has already been proven to be safe, predictable and reproducable, with expanding indications [25,26]. Our first-in-field pilot study offers insight into the treatment of advanced stage, bulky and surgically inoperable STSs with bleomycin based ECT through VEG electrodes.

Previous publications on STS ECT mostly included case reports [27,28] along with a 2014 phase II study by Campana et al. evaluating the efficacy of standard ECT in 30 patients with superficial STS (not exceeding 3 cm in depth) and achieving 85.3% OR rate [29]. Our study exclusively included deep-seated STSs (tumour depth of 3 cm<), hence increased depth and higher tumour volume may explain lower OR (PR: 71.42%). Results of Campana et al. for toxicity after ECT showed local soft tissue necrosis and ulceration in the majority of cases (76.5% and 52.9%), correlating with the present study in which Grade 2 ulcerations were found in 6 cases (85.71%).

Deep-seated tumours involve lesions not eligible for standard ECT simply due to the fact that the deepest tumour margin is out of reach for standard electrodes. VEG electrodes on the other hand include long linear probes ranging from 12-24 cm, with active tips of 30, or 40 mm,

which are able to reach target lesions and if necessary, may be repositioned deeper in order to reach target depth and maintain safety margins.

Our prospective pilot study included seven patients with deep-seated STS and detailed initial treatment outcomes of BLM-based VEG ECT. The low number of patients is due to the fact that STSs are rare occurring tumours, with a low yearly incidence (6/100.000) [30].

We evaluated patients previously receiving various oncological treatment, those eventually not candidates for further traditional interventions. Previously published studies did not include cases treated with similar parameters, and mostly described series managed with standard electrodes [29].

Since bulky, large volume tumours were treated, in order to cover complete tumour extent, electrode repositioning was carried out in 6 cases (85.71%). However the need for repositioning is a common phenomenon during VEG ECT, Simioni et al. confirmed a 60% repositioning rate during VEG electrode placement for sufficient current delivery and tumour coverage [18]. Besides the effect which the train of electric currents (with sufficient amplitude and intensity) induce on tumour tissue, successful ECT treatment strongly depends on tissue inhomogenity. This refers to the observation, that during delivery of electric currents, electric field distribution also differs within the tumour, resulting in modification of the electric effect and resulting in different tumour response within the same tumour tissue [31]. Tissue inhomogenity poses as a crucial phenomenon, possibly accounting for distinct tumour response within the same STS, making ECT treatment even more diverse and specific.

Tumour size (largest diameter), -volume and –depth (tumour size-volume-depth: tSVD) evaluation was performed pre- and postoperatively in each case to assess local control. Largest tumour volume and – depth was found in PR cases (tSVD: 8.7 cm, 131.13 cm3, 10.842 cm) which interestingly contradicts results of a previous trial by Mali et al., confirming that larger tumour size (3 cm<)- due to increased heterogenous drug distribution and reduced effect of electroporation- may reduce effectiveness of ECT [32]. Since all lesions were advanced and surgically inoperable, reaching complete response (CR) was not the intent of the current treatment series, hence the relatively high PR rate seems to meet the purpose of treatment (local control).

Surgical resection is still the mainstay for STSs, and reaching R0 resection with clear surgical margins is paramount and directly related to overall survival and local control [33]. In addition to surgical margins, the intrinsic biological features of a certain STS also influence local/distant recurrence [34]. In the systematic meta-analysis by Pervaiz et al., including 17 trials (1700 patients with 296 local- and 553 distant recurrence of STS), significant decrease in local recurrence was noted with adjuvant doxorubicin-based chemotherapy (0.73 OR, 95% CI, 0.56-0.94; *P* = .02) and significantly reduced distant recurrence rate was found with doxorubicin alone (0.69 OR, 95% CI, 0.56-0.86; *P* = .001) and combined with ifosfamide (0.61 OR,95% CI, 0.41-0.92; *P* = .02) [35].

Overall survival (OS) and local progression-free survival (LPFS) strongly depend on complete surgical resection. Radiation therapy may be administered in an adjuvant, or neoadjuvant setting, with studies showing improved local control with postoperative radiation, however no significant changes in OS [36]. Chemotherapy for adult STS remains controversial, and has shown significant benefits in downstaging, or downsizing in selected cases. Novel treatment strategies have mainly focused on targeted therapies and immunotherapy. Pembrolizumab

and nivolumab besides proven successful in the treatment of NSCLC (non-small cell lung cancer), malignant melanoma, lymphoma, and urothelial carcinoma, have unfortunately shown only modest results in cases of STSs [37]. Nevertheless immunotherapy applied in combination with ECT has been reported to boost efficacy of ECT, thus facilitating tumour

et al. compared ECT+ soluble IL-2 vs ECT alone in mice with fibrosarcoma and found significant tumour regression with the combined treatment [39]. The current study included one patient who received ECT combined with immunotherapy and reached PR with the highest rate of tumour regression (-75.48%); (Table 5). However all of our patients were heavily treated before the current ECT session (Table 4), hence each case involved prolonged previous treatment courses and advanced lesions which may have also contributed to reduced OR.

With the steady evolvement of novel treatment options, applied therapy for STS remains promising, nonetheless most patients eventually have to deal with uncontrolled tumour overgrowth. Rapid growth patterns and high probability of recurrence remain a major drawback of STSs and make treatment highly specific. A 2011 prognostic model dealing with factors influencing recurrence and distant metastasis highlights four factors which may influence STS advancement. The model, considering size, invasion, necrosis and growth (SING) as predictive factors confirmed that tumour size may be used as an indipendent prognostic factor and thus make STSs highly prone to recurrence [40]. The present study included lesions with a median tumour volume of 131.13 cm3, which may also confirm predictive value of SING since all lesions received a wide variety of previous treatments and still showed bulky recurrence.

The current study included advanced stage, inoperable STSs, hence efficacy of ECT treatment may readily be valued in comparison with chemotherapy (6-month progression-free survival: 0-51%) [41], radiation therapy (5-year local control: ~ 33%) [42], or HILP (hyperthermic isolated limb perfusion) (local/regional recurrence: 11-48%) [43].

Limitations of the study include relatively low number of included patients, however the low incidence of soft tissue sarcomas should also be taken into account. Treated tumours showed broad variations in histology and localisation which surely influenced evaluation of treatment outcomes. The majority of patients received additional systemic therapy during the follow-up period, which made objective evaluation of treatment response even more complicated.

An interesting question needing further debate is the follow-up of patients. RECIST guidelines gives us clear instructions on how radiological follow-up should be carried out. However in cases of deep-seated soft tissue sarcomas the choice of imaging modalities is not always straigh-forward. MRI is the recommended modality in most cases, although PET-CT would probably provide a more accurate pattern of follow-up imaging, since it would be able to show a more precise and distinguishable image on post-treatment necrotic tissue and viable tumour tissue. In order to maintain accurate follow-up of STS patients, such issues regarding postECT treatment imaging should be further addressed.

Since publications on STS ECT are still scarce and only standard ECT treatment for superficial tumours have been reported, the current study is found to be the first to report outcomes on BLM-based VEG ECT. Multi-institutional studies and prospective randomized trials are needed to properly assess treatment outcomes and long term results for BLM-based VEG ECT for advanced stage STSs.

Conclusions

Although the exact role of BLM-based VEG ECT in the management of difficult to treat STSs

the complex treatment of advanced, surgically inoperable tumours. Our initial results although preliminary, can serve as a practical guide for further improving current treatment modalities.

Author Contributions

Concept: A.O, G.E.K, J.O, Gy.L; methodology: A.O, G.E.K, A.N, J.O; validation: A.O, G.E.K, Gy.L, J.O; investigation: A.O, G.E.K, J.O; resources: A.O, G.E.K, Gy.L, J.O; data curation: A.O, L.R.K; B.D; Z.G.V; Zs.B; writing—original draft preparation: A.O, G.E.K; J.O, K.B writing—review and editing: A.O, G.E.K, Gy.L, J.O, K.H; supervision: G.E.K, Gy.L, J.O; project administration: A.O; funding acquisition: O.A, Gy.L. All authors have read and agreed to the published version of the manuscript.

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References

1. Fletcher, CDM; Bridge, JA; Hogendoorn, PCW; Lyon, MF. World Health Organization classification of tumours of soft tissue and bone. 4th ed. Lyon: IARC Press; 2013.
2. Jemal, A; Tiwari, RC; Murray, T; Ghafoor, A; Samuels, A; Ward, E; Feuer, EJ; Thun, MJ; American Cancer Society. Cancer statistics, 2004. *CA Cancer J Clin* 2004, *54*, 8-29. doi: 10.3322/canjclin.54.1.8. PMID: 14974761.
3. Lawrence, W Jr; Donegan, WL; Ntarajan, N; Mettlin, C; Beart, R; Winchester, D. Adult soft tissue sarcomas. A pattern of care survey of the American College of Surgeons. *Ann Surg* 1987, *205*, 349–359.
4. Brouns, F; Stas, M; De Wever, I. Delay in diagnosis of soft tissue sarcomas. *Eur J Surg Oncol* 2003, *29*, 440-5. doi: 10.1016/s0748-7983(03)00006-4. PMID: 12798748.

5. Gerrand, C; Francis, M; Dennis, N; Charman, J; Lawrence, G; Evans, T et al. Routes to diagnosis for sarcoma - describing the sarcoma patient journey. *Eur J Surg Oncol* 2015, *41*, 1393–9.
6. The ESMO/European Sarcoma Network Working Group. Soft tissue and visceral

Ann Oncol 2014, 25 Suppl 3:iii102–iii112.
7. Campana, LG; Bianchi, G; Mocellin, S; Valpione, S; Campanacci, L; Brunello, A; Donati, D; Sieni, E; Rossi, CR. Electrochemotherapy treatment of locally advanced and metastatic soft tissue sarcomas: results of a non-comparative phase II study. *World J Surg* 2014, *38*, 813-822. doi: 10.1007/s00268-013-2321-1. PMID: 24170155.
8. Belehradek, M; Domenge, C; Luboinski, B; Orlowski, S; Belehradek, J Jr; Mir LM. Electrochemotherapy, a new antitumor treatment. First clinical phase I-II trial. *Cancer* 1993, *72*, 3694-700. doi: 10.1002/1097-0142(19931215)72:12<3694::aid-cncr2820721222>3.0.co;2-2. PMID: 7504576.
9. Matthiessen, LW; Chalmers, RL; Sainsbury, DC; Veeramani, S; Kessell, G; Humphreys, AC; Bond, JE; Muir, T; Gehl J. Management of cutaneous metastases using electrochemotherapy. *Acta Oncol* 2011, *50*, 621-629. doi: 10.3109/0284186X.2011.573626. PMID: 21574833; PMCID: PMC3130997.
10. Bertino, G; Sersa, G; De Terlizzi, F; Occhini, A; Plaschke, CC; Groselj, A; Langdon, C; Grau, JJ; McCaul, JA; Heuveling, D; Cemazar, M; Strojan, P et al. European Research on Electrochemotherapy in Head and Neck Cancer (EURECA) project: Results of the treatment of skin cancer. *Eur J Cancer* 2016, *63*, 41-52. doi: 10.1016/j.ejca.2016.05.001. Epub 2016 Jun 4. PMID: 27267144.
11. Sersa, G; Jarm, T; Kotnik, T; Coer, A; Podkrajsek, M; Sentjurc, M; Miklavcic, D; Kadivec, M; Kranjc, S; Secerov, A et al. Vascular disrupting action of electroporation and electrochemotherapy with bleomycin in murine sarcoma. *Br J Cancer* 2008, *98*, 388-98. doi: 10.1038/sj.bjc.6604168. Epub 2008 Jan 8. PMID: 18182988; PMCID: PMC2361464.
12. Sersa, G; Mascherini, M; Di Prata, C; Odili, J; de Terlizzi, F; McKenzie, GAG; Clover, AJP; Bertino, G; Spina, R; Groselj, A et al. Outcomes of older adults aged 90 and over with cutaneous malignancies after electrochemotherapy with bleomycin: A matched cohort analysis from the InspECT registry. *Eur J Surg Oncol* 2021, *47*, 902-912. doi: 10.1016/j.ejso.2020.10.037. Epub 2020 Nov 6. PMID: 33183930.
13. Kis, EG; Baltás, E; Ócsai, H; Vass, A; Németh, IB; Varga, E; Oláh, J; Kemény, L; Tóth-Molnár E. Electrochemotherapy in the treatment of locally advanced or recurrent eyelid-periocular basal cell carcinomas. *Sci Rep* 2019, *9*, 4285. doi: 10.1038/s41598-019-41026-2. PMID: 30862897; PMCID: PMC6414678.
14. Kunte, C; Letulé, V; Gehl, J; Dahlstroem, K; Curatolo, P; Rotunno, R; Muir, T; Occhini, A; Bertino, G; Powell, B et al. InspECT (the International Network for Sharing Practices on Electrochemotherapy). Electrochemotherapy in the treatment of metastatic malignant melanoma: a prospective cohort study by InspECT. *Br J Dermatol* 2017, *176*, 1475-1485. doi: 10.1111/bjd.15340. Epub 2017 Apr 26. PMID: 28118487.
15. Ágoston, D.; Baltás, E.; Ócsai, H.; Rátkai, S.; Lázár, P.G.; Korom, I.; Varga, E.; Németh, I.B.; Dósa-Rácz Viharosné, É.; Gehl, J.; Oláh, J.; Kemény, L.; Kis, E.G. Evaluation of Calcium Electroporation for the Treatment of Cutaneous Metastases: A Double Blinded Randomised Controlled Phase II Trial. *Cancers* 2020, *12*, 179.

16. Clover, AJP; de Terlizzi, F; Bertino, G; Curatolo, P; Odili, J; Campana, LG; Kunte, C; Muir, T; Brizio, M; Sersa, G et al. Electrochemotherapy in the treatment of cutaneous malignancy: Outcomes and subgroup analysis from the cumulative results from the pan-European International Network for Sharing Practice in Electrochemotherapy

40. doi: 10.1016/j.ejca.2020.06.020. Epub 2020 Aug 21. PMID: 32836172.
17. Djokic, M; Cemazar, M; Bosnjak, M; Dezman, R; Badovinac, D; Miklavcic, D; Kos, B; Stabuc, M; Stabuc, B; Jansa, R et al. A Prospective Phase II Study Evaluating Intraoperative Electrochemotherapy of Hepatocellular Carcinoma. *Cancers* 2020, *12*, 3778. doi: 10.3390/cancers12123778. PMID: 33333941; PMCID: PMC7765454.
18. Simioni, A; Valpione, S; Granziera, E; Rossi, CR; Cavallin, F; Spina, R; Sieni, E; Aliberti, C; Stramare, R; Campana, LG. Ablation of soft tissue tumours by long needle variable electrode-geometry electrochemotherapy: final report from a single-arm, single-centre phase-2 study. *Sci Rep* 2020, *10*, 2291. doi: 10.1038/s41598-020-59230-w. PMID: 32042142; PMCID: PMC7010705.
19. Doyle, LA. Sarcoma classification: an update based on the 2013 World Health Organization Classification of Tumors of Soft Tissue and Bone. *Cancer* 2014, *120*, 1763-1774. doi: 10.1002/cncr.28657. Epub 2014 Mar 19. PMID: 24648013.
20. Campana, LG; Miklavcic, D; Bertino, G; Marconato, R; Valpione, S; Imarisio, I; Dieci, MV; Granziera, E; Cemazar, M; Alaibac, M et al. Electrochemotherapy of superficial tumors - Current status: Basic principles, operating procedures, shared indications, and emerging applications. *Semin Oncol* 2019, *46*, 173-191. doi: 10.1053/j.seminoncol.2019.04.002. Epub 2019 May 9. PMID: 31122761.
21. Stacchiotti, S; Frezza, AM; Blay, JY; Baldini, EH; Bonvalot, S; Bovée, JVMG; Callegaro, D; Casali, PG; Chiang, RC; Demetri, GD et al. Ultra-rare sarcomas: A consensus paper from the Connective Tissue Oncology Society community of experts on the incidence threshold and the list of entities. *Cancer* 2021. doi: 10.1002/cncr.33618. Epub ahead of print. PMID: 33910263.
22. Karavasilis, V; Seddon, BM; Ashley, S; Al-Muderis, O; Fisher, C; Judson, I. Significant clinical benefit of first-line palliative chemotherapy in advanced soft-tissue sarcoma: retrospective analysis and identification of prognostic factors in 488 patients. *Cancer* 2008, *112*, 1585-1591. doi: 10.1002/cncr.23332. PMID: 18278813.
23. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, Dancey J, Arbuck S, Gwyther S, Mooney M et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer* 2009, *45*, 228-47. doi: 10.1016/j.ejca.2008.10.026. PMID: 19097774.
24. Gehl, J; Sersa, G; Matthiessen, LW; Muir, T; Soden, D; Occhini, A; Quaglino, P; Curatolo, P; Campana, LG; Kunte, C et al. Updated standard operating procedures for electrochemotherapy of cutaneous tumours and skin metastases. *Acta Oncol* 2018, *57*, 874-882. doi: 10.1080/0284186X.2018.1454602. Epub 2018 Mar 25. PMID: 29577784.
25. Izzo, F; Granata, V; Fusco, R; D'Alessio, V; Petrillo, A; Lastoria, S; Piccirillo, M; Albino, V; Belli, A; Tafuto, S et al. Clinical Phase I/II Study: Local Disease Control and Survival in Locally Advanced Pancreatic Cancer Treated with Electrochemotherapy. *J Clin Med* 2021, *10*, 1305. doi: 10.3390/jcm10061305. PMID: 33810058; PMCID: PMC8005134.
26. Strojan, P; Grošelj, A; Serša, G; Plaschke, CC; Vermorken, JB; Nuyts, S; de Bree, R; Eisbruch, A; Mendenhall, WM; Smee, R et al. Electrochemotherapy in Mucosal Cancer

of the Head and Neck: A Systematic Review. *Cancers (Basel)* 2021, *13*, 1254. doi: 10.3390/cancers13061254. PMID: 33809141; PMCID: PMC7999968.

27. de Bree, R; Tijink, BM; van Groeningen, CJ; Leemans, CR. Electroporation therapy in soft tissue sarcoma: a potentially effective novel treatment. *Sarcoma* 2006, PMC1557797.
28. Shimizu, T; Nikaido, T; Gomyo, H; Yoshimura, Y; Horiuchi, A; Isobe, K; Ebara, S; Takaoka, K. Electrochemotherapy for digital chondrosarcoma. *J Orthop Sci* 2003, *8*, 248-251. doi: 10.1007/s007760300043. PMID: 12665967.
29. Hui, JYC. Epidemiology and etiology of sarcomas. *Surg Clin North Am* 2016, *96*, 901–914.
30. Casali, PG; Abecassis, N; Aro, HT; Bauer, S; Biagini, R; Bielack, S; Bonvalot, S; Boukovinas, I; Bovee, JVMG; Brodowicz, T et al. ESMO Guidelines Committee and EURACAN. Soft tissue and visceral sarcomas: ESMO-EURACAN Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2018, *29*, 268-269. doi: 10.1093/annonc/mdy321. Erratum for: Ann Oncol. 2018 Oct 1;29(Suppl 4):iv51-iv67. PMID: 30285214.
31. Campana, LG; Bullo, M; Di Barba, P; Dughiero, F; Forzan, M; Mognaschi, ME; Sgarbossa, P; Tosi, AL; Bernardis, A; Sieni, E. Effect of Tissue Inhomogeneity in Soft Tissue Sarcomas: From Real Cases to Numerical and Experimental Models. *Technol Cancer Res Treat* 2018, 17:1533033818789693. doi: 10.1177/1533033818789693. PMID: 30045667; PMCID: PMC6071161.
32. Mali, B; Miklavcic, D; Campana, LG; Cemazar, M; Sersa, G; Snoj, M; Jarm, T. Tumor size and effectiveness of electrochemotherapy. *Radiol Oncol* 2013, *47*, 32-41. doi: 10.2478/raon-2013-0002. Epub 2013 Feb 1. PMID: 23450195; PMCID: PMC3573832.
33. Zhang, L; Akiyama, T; Fukushima, T; Iwata, S; Tsuda, Y; Takeshita, K; Kawai, A; Tanaka, S; Kobayashi, H. Prognostic factors and impact of surgery in patients with metastatic soft tissue sarcoma at diagnosis: A population-based cohort study. *Jpn J Clin Oncol* 2021, *51*, 918-926. doi: 10.1093/jjco/hyab033. PMID: 33774673.
34. Biau, DJ; Ferguson, PC; Chung, P; Griffin, AM; Catton, CN; O'Sullivan, B; Wunder, JS. Local recurrence of localized soft tissue sarcoma: a new look at old predictors. *Cancer* 2012, *118*, 5867-77. doi: 10.1002/cncr.27639. Epub 2012 May 30. PMID: 22648518.
35. Pervaiz, N; Colterjohn, N; Farrokhyar, F; Tozer, R; Figueredo, A; Ghert, M. A systematic meta-analysis of randomized controlled trials of adjuvant chemotherapy for localized resectable soft-tissue sarcoma. *Cancer* 2008, *113*, 573-81. doi: 10.1002/cncr.23592. PMID: 18521899.
36. Nowicki, TS; Hu-Lieskovan, S; Ribas, A. Mechanisms of Resistance to PD-1 and PD-L1 Blockade. *Cancer J* 2018, *24*, 47-53. doi: 10.1097/PPO.0000000000000303. PMID: 29360728; PMCID: PMC5785093.
37. Longo, F; Perri, F; Caponigro, F; Della Vittoria Scarpati, G; Guida, A; Pavone, E; Aversa, C; Muto, P; Giuliano, M; Ionna, F et al. Boosting the Immune Response with the Combination of Electrochemotherapy and Immunotherapy: A New Weapon for Squamous Cell Carcinoma of the Head and Neck? *Cancers (Basel)* 2020, *12*, 2781. doi: 10.3390/cancers12102781. PMID: 32998297; PMCID: PMC7601050.
38. Campana LG, Peric B, Mascherini M, Spina R, Kunte C, Kis E, Rozsa P, Quaglino P, Jones RP, Clover AJP, Curatolo P, Giorgione R, Cemazar M, Terlizzi F, Bosnjak M, Sersa G. Combination of Pembrolizumab with Electrochemotherapy in Cutaneous Metastases

from Melanoma: A Comparative Retrospective Study from the InspECT and Slovenian Cancer Registry. Cancers (Basel). 2021 Aug 25;13(17):4289. doi: 10.3390/cancers13174289. PMID: 34503099; PMCID: PMC8428335.

39. Mir, LM; Roth, C; Orlowski, S; Quintin-Colonna, F; Fradelizi, D; Belehradek, J Jr; histoincompatible cells secreting interleukin-2. *J Immunother Emphasis Tumor Immunol* 1995, *17*, 30-8. doi: 10.1097/00002371-199501000-00004. PMID: 7537154.
40. Pervaiz, N; Colterjohn, N; Farrokhyar, F; Tozer, R; Figueredo, A; Ghert, M. A systematic meta-analysis of randomized controlled trials of adjuvant chemotherapy for localized resectable soft-tissue sarcoma. *Cancer* 2008, *113*, 573-81. doi: 10.1002/cncr.23592. PMID: 18521899.
41. Penel, N; Van Glabbeke, M; Marreaud, S; Ouali, M; Blay, JY; Hohenberger, P. Testing new regimens in patients with advanced soft tissue sarcoma: analysis of publications from the last 10 years. *Ann Oncol* 2011, *22*, 1266-1272. doi: 10.1093/annonc/mdq608. Epub 2010 Dec 23. PMID: 21183581.
42. Tepper, JE; Suit, HD. Radiation therapy alone for sarcoma of soft tissue. *Cancer* 1985, *56*, 475-479. doi: 10.1002/1097-0142(19850801)56:3<475::aid-cncr2820560311>3.0.co;2-s. PMID: 4005809.
43. Deneve, JL; Zager, JS. Isolated regional therapy for advanced extremity soft tissue sarcomas. *Surg Oncol Clin N Am* 2012, *21*, 287-299. doi: 10.1016/j.soc.2011.11.003. Epub 2011 Dec 13. PMID: 22365520.

Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐ The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Highlights

- Bleomycin-based electrochemotherapy with variable electrode geometry for deep-seated, advanced stage, surgically inoperable soft tissue sarcomas
- 71.42% ORR (objective response rate)
- Improved quality of life and subjective complaints
- Promising treatment modality where previous treatment options have been exploited